



Madhu Anant, Ph.D., RAC
Senior Director, Regulatory Affairs
Valeant Pharmaceuticals North America, LLC
700 Route 202/206 North
Bridgewater, NJ 08807-6935

RE: NDA # 021894
XENAZINE[®] (tetrabenazine) Tablets, for Oral Use
MA # 90

Dear Dr. Anant:

The Office of Prescription Drug Promotion (OPDP), Division of Professional Drug Promotion (DPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a Huntington's disease (HD) patient assessment video entitled, "Patient Case 1:Leslie" (patient assessment video) for XENAZINE[®] (tetrabenazine) Tablets for Oral Use (Xenazine). This video is located on a page of the Medscape.com website¹, which was submitted by Valeant Pharmaceuticals North America, LLC (Valeant)² as part of Xenazine internet promotion on WebMD (XZN206R1) under cover of Form FDA 2253.

The patient assessment video and the webpage where the patient assessment video is located, are false and misleading because they overstate the efficacy, omit material facts, and omit and minimize the serious risks of Xenazine. Thus, the patient assessment video and the webpage where the patient assessment video is located misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a) & (n); 321(n). See 21 CFR 202.1 (e)(5), (e)(6)(i) & (e)(7)(viii).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Xenazine.³ According to its FDA-approved product labeling (PI):

¹ HD patient assessment video entitled "Patient Case 1:Leslie" at <http://www.medscape.com/infosite/xenazine/article-1#a2> (last accessed March 13, 2012). This webpage includes information that it was "[D]eveloped under direction and sponsorship of Lundbeck, Inc." Xenazine[®] is currently marketed by Lundbeck, Inc.

² Xenazine[®] is a registered trademark of Biovail Laboratories International (Barbados) S.R.L.. On March 8, 2011, Biovail Laboratories International (Barbados) SRL was amalgamated into Valeant International (Barbados) SRL.

³ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

XENAZINE is indicated for the treatment of chorea associated with Huntington's disease.

Xenazine is associated with a number of serious risks, including a Boxed Warning on the increased risk of depression and suicidality. According to its PI, Xenazine is contraindicated in patients who are actively suicidal, patients with untreated or inadequately treated depression, patients with impaired hepatic function, and patients taking monoamine oxidase inhibitors (MAOIs) and reserpine. Additionally, there are Warnings and Precautions regarding clinical worsening and adverse effects, establishing proper dosing of Xenazine, genotyping for CYP2D6 expression, Neuroleptic Malignant Syndrome (NMS), akathisia, restlessness, agitation, parkinsonism, dysphagia, sedation and somnolence, interaction with alcohol, QTc prolongation, concomitant use of neuroleptic drugs, hypotension and orthostatic hypotension, hyperprolactinemia, tardive dyskinesia (TD), use in patients with concomitant illnesses, and binding to melanin-containing tissues. The most common adverse reactions with Xenazine are (>10% and at least 5% greater than placebo) sedation/somnolence, fatigue, insomnia, depression, akathisia, anxiety, and nausea.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience.

The patient assessment video presents Leslie, a patient diagnosed with Huntington's disease. The pre-treatment portion of the video clearly shows that before treatment with Xenazine Leslie had difficulty maintaining his balance and walking. For example, he falls backward and is unable to steady himself when the physician pulls on his shoulder to assess his postural stability on the retropulsion pull test. Additionally, during the walking test, Leslie has an unsteady gait, sways, and has difficulty maintaining balance when changing direction.

The post-treatment portion of the video shows Leslie's improvement after 10 weeks on Xenazine. Leslie is now able to maintain his posture and does not fall backward during the retropulsion pull test. He does not sway and is able walk in a straight line. Leslie is also able to preserve his balance, as demonstrated by his ability to walk heel-to-toe during the tandem walking test.

The before and after Xenazine patient presentations are misleading because they suggest that treatment with Xenazine will lead to significant improvements in balance, walking, and postural stability in patients with HD, when such benefits have not been demonstrated by substantial evidence. According to the CLINICAL STUDIES section of the PI:

The primary efficacy endpoint was the Total Chorea Score, an item of the Unified Huntington's Disease Rating Scale (UHDRS). On this scale, chorea is rated from 0 to 4 (with 0 representing no chorea) for 7 different parts of the body. The total score ranges from 0 to 28. . . . Total Chorea Scores for subjects in the drug group declined

by an estimated 5.0 units during maintenance therapy (average of Week 9 and Week 12 scores versus baseline), compared to an estimated 1.5 units in the placebo group. The treatment effect of 3.5 units was statistically significant.

Although Xenazine has demonstrated improvement in Total Chorea Score, it has not been shown to provide a benefit on other symptoms of HD such as balance, walking or postural stability. An improvement in chorea is not associated with an improvement in balance, walking or postural stability, and Total Chorea Score does not include any assessment of these symptoms. In fact, the pivotal trial supporting the approval of Xenazine failed to demonstrate a statistically significant benefit for Xenazine in the UHDRS Total Motor score, a domain of the UHDRS that assesses motor function and which includes the assessment of Total Chorea Score and 14 other items such as gait, tandem walking, and retropulsion pull test. We note that the following statements are included on the webpage where the patient assessment video is located, **“Xenazine does not cure the cause of HD chorea and does not treat the other symptoms of HD”** (emphasis original) and “These are videos of actual patients being evaluated by their physician. Individual results may vary. Xenazine may not be effective in reducing choreic movements in all HD patients.” However, these statements do not mitigate the above misleading presentation in the patient assessment video.

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The patient assessment video presents the following information on dosing and administration for Xenazine:

“The dose of Xenazine should be individualized by starting low and going slow by 12.5 mg increments weekly until a patient experiences clinical effect without intolerable adverse events. The patient returned after 10 weeks at which time his chorea was well-controlled with Xenazine.”

This dosing presentation is misleading because it omits important material information related to dosing and administration of Xenazine, which is critical for the safe use of this product. Specifically, this dosing presentation fails to communicate the recommended starting and maximum dose of Xenazine, the frequency of administration, dosing recommendations for extensive, intermediate, and poor metabolizers of CYP2D6, and dosing considerations for those who take strong CYP2D6 inhibitors. We note that the webpage where the patient assessment video is located includes some dosing information and a link titled, “Dosing and Titration.” However, the inclusion of this limited amount of dosing information and a link to a more complete presentation of the dosing information, on the webpage where the video is located, does not correct the misleading omission of material information from this dosing presentation.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to present risk information with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. Promotional materials are also misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The patient assessment video, which is 3 minutes and 55 seconds in duration, presents many claims regarding the efficacy of Xenazine but minimizes the risks of Xenazine by failing to convey any risks associated with Xenazine during this audio-visual presentation. For example, the patient assessment video omits any discussion of serious risks, such as the boxed warning, contraindications, warnings and precautions associated with Xenazine. We acknowledge that the webpage where the patient assessment video is located includes some risk information for Xenazine, however this risk presentation is relegated to the bottom portion of the webpage, below the patient assessment video in read-only text format, where it is unlikely to draw the viewer's attention. Therefore, this overall presentation misleadingly minimizes the serious risks associated with Xenazine because it fails to convey this important risk information with a prominence and readability reasonably comparable to the claims of effectiveness. The overall effect of the risk presentation undermines the communication of important risk information for Xenazine, thereby misleadingly suggesting that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Furthermore, the webpage where the patient assessment video is located completely omits the risk of clinical worsening and adverse effects associated with Xenazine and the increased risk of somnolence and sedation with concomitant use of alcohol or other sedating drugs.

In addition, the webpage minimizes the risks of NMS, akathisia, restlessness, agitation, parkinsonism, and dysphagia associated with Xenazine by failing to include important material information regarding these Warnings and Precautions. Specifically, the webpage fails to include that NMS can be potentially fatal, the clinical manifestations of NMS, and the need to discontinue Xenazine if NMS occurs. The webpage also fails to disclose the need for dose reduction or discontinuation of Xenazine if akathisia, restlessness, agitation or parkinson occurred during Xenazine treatment, and the potential risk of aspiration pneumonia due to dysphagia.

According to the WARNINGS and PRECAUTIONS section of the PI (in pertinent part),

5.5 Risk of Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with XENAZINE Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and

evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. . . .

The management of NMS should include (1) immediate discontinuation of XENAZINE and other drugs not essential to concurrent therapy

5.6 Risk of Akathisia, Restlessness, and Agitation

. . . . Patients receiving XENAZINE should also be monitored for signs and symptoms of restlessness and agitation, as these may be indicators of developing akathisia. If a patient develops akathisia, the XENAZINE dose should be reduced; however, some patients may require discontinuation of therapy.

5.7 Risk of Parkinsonism

. . . . Drug-induced parkinsonism has the potential to cause more functional disability than untreated chorea for some patients with Huntington's disease. If a patient develops parkinsonism during treatment with XENAZINE, dose reduction should be considered; in some patients, discontinuation of therapy may be necessary.

5.8 Risk of Dysphagia

. . . . Some of the cases of dysphagia were associated with aspiration pneumonia.

By failing to present important material information for these risks, the webpage misleadingly suggests that Xenazine is safer than has been demonstrated.

Conclusion and Requested Action

For reasons discussed above, the patient assessment video, and the webpage where the patient assessment video is located, misbrand Xenazine in violation of the FD&C Act, 21 U.S.C. 352(a) & (n); 321(n). See 21 CFR 202.1(e)(5), (e)(6)(i) & (e)(7)(viii).

OPDP requests that Valeant immediately cease the dissemination of violative promotional materials for Xenazine such as those described above. Please submit a written response to this letter on or before July 6, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Xenazine that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and

elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA # 90 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Xenazine comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

{See appended electronic signature page}

Mathilda Fienkeng, PharmD
Team Leader (Acting)
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/s/

QUYNH-VAN TRAN

06/20/2012

MATHILDA K FIENKENG

06/21/2012